When Lightning Strikes Twice in Pediatrics: Case Report and Review of Recurrent Myocarditis

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Myocarditis is an important but incompletely understood cause of cardiac dysfunction. Children with fulminant myocarditis often require inotropic or mechanical circulatory support, and researchers in some studies suggest that up to 42% of children who die suddenly have evidence of myocarditis. Recurrent myocarditis is extremely rare, and the vast majority of reported cases involve adult patients. Pediatric providers who suspect a recurrence of myocarditis have limited evidence to guide patient management because the literature in this domain is sparse. Here we present a unique, illustrative pediatric case of recurrent myocarditis. A 14-year-old boy presented for the second time in 2 years with a clinical history strongly suggestive of myocarditis. Although myocarditis was suggested in the results of cardiac MRI, no pathogen was identified during his first presentation. During his second episode of myocarditis, parvovirus was confirmed by polymerase chain reaction testing of an endomyocardial specimen that also met Dallas criteria for myocarditis. With each presentation, he had decreased ventricular function that subsequently normalized. To the best of our knowledge, there are no reports of recurrent myocarditis in children in whom the diagnosis was confirmed by using MRI and/or biopsy data. Reviewing this distinctive case and the existing literature may help characterize this entity and raise awareness among care providers.

Myocarditis is an important but poorly understood cause of cardiac dysfunction. Although the presentation of myocarditis can be benign, a delayed or missed diagnosis may lead to significant morbidity and mortality in select cases. Fulminant myocarditis can rapidly progress to hemodynamic collapse and death. Researchers in some studies suggest that up to 42% of pediatric sudden deaths have been associated with myocarditis.[1–4] It has also been reported that approximately a quarter of all children with myocarditis require some form of mechanical circulatory support.[5] In addition to guiding acute management, defining the cause of cardiac dysfunction can be important for long-term prognosis, especially if a viral cause is identified.[6] Although more than half of children with myocarditis who survive the initial course do recover, there may be the potential for recurrence in an unlucky few.[7–9]

Recurrent myocarditis is a rare phenomenon with only a handful of reports in the literature. Here we review the current literature and present a unique, illustrative pediatric case of recurrent myocarditis with the aim of guiding other care providers when faced with a similar scenario.

CASE REPORT

A previously healthy 14-year-old boy presented to his primary care

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Dr Floyd drafted the manuscript; Drs Lal, Molina, Puchalski, and Miller participated in the concept, drafting, and revising of the manuscript; Dr May served as both mentor to Dr Floyd and senior author, and she participated in the concept, drafting, and revising of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2016-4096

Accepted for publication May 4, 2017

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Floyd A, Lal A, Molina K, et al. When Lightning Strikes Twice in Pediatrics: Case Report and Review of Recurrent Myocarditis. *Pediatrics.* 2018;141(3):e20164096

physician, complaining of acute, severe substernal chest pain as well as orthopnea and diaphoresis. The symptoms were preceded by 2 days of fever, cough, and sore throat. He was treated with ibuprofen for presumed musculoskeletal chest pain but was seen in the emergency department (ED) the next morning with worsening chest pain. In the ED, his vital signs were reassuring and his physical examination was unremarkable with the exception of pallor. An electrocardiogram (ECG) revealed mild, diffuse ST segment elevation as well as T wave inversion in the lateral leads. A complete blood cell count revealed a normal white blood cell (WBC) count but with 48% neutrophils and 20% bands. The troponin-I, creatine kinase-MB (CKMB), and creatine kinase (CK) levels were markedly elevated at 17.62 ng/mL (normal 0.0–0.04 ng/mL), 86.4 μg/L (normal 0.0–5 μg/L), and 978 U/L (normal 60–335 U/L), respectively. An echocardiogram revealed low-normal left ventricular (LV) systolic function and an ejection fraction (EF) of 55%, without segmental wall motion abnormalities or ventricular dilation (left ventricular end-diastolic internal dimension [LVIDd]: 4.27 cm, *z* score −1.62). With a clinical diagnosis of myocarditis, he was admitted to the cardiac ICU and received a single dose of 1 g/kg of intravenous immunoglobulin. Cardiac MRI revealed anteroseptal and midventricular edema suggestive of myocarditis.[10] The results of serum viral studies (including parvovirus immunoglobulin M titers) as well as toxoplasmosis and mycoplasma testing were negative. His chest pain resolved, his ECG and echocardiogram results normalized (EF 65%), and he was discharged after 4 days with markedly improved troponin levels (0.91 ng/mL). He was doing well at routine follow-up visits and was without chest pain. His interim echocardiograms demonstrated normal ventricular function.

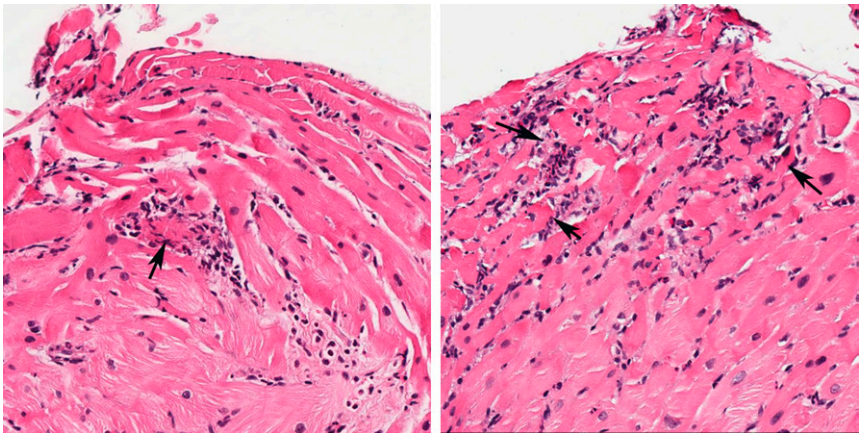

FIGURE 1
EMB specimens stained with hematoxylin and eosin, revealing mixed inflammatory infiltrate with convincing foci of myocyte damage (arrows) that is consistent with acute lymphocytic myocarditis. Immunostaining for leukocyte markers are not routinely performed in our laboratory.

Thirteen months later, this patient re-presented to the ED with dull, central chest and left arm pain. Three days before, he had sore throat, fever, and myalgia. Once again, his physical examination was unremarkable. A complete blood cell count revealed a normal WBC count but with 41% neutrophils and 29% bands. His C-reactive protein level was elevated at 4.1 mg/dL and his ECG revealed ST elevation in the anterolateral and inferior leads. Results of a urine drug screen were negative. He was admitted to the hospital with a troponin level of 22 ng/mL, and a limited echocardiogram revealed decreased LV systolic function (EF 42%) with normal chamber dimensions (LVIDd: 4.89 cm, *z* score −0.19). He again received intravenous immunoglobulin (2 mg/kg) and later started on metoprolol for nonsustained ventricular tachycardia. With a rising troponin level (up to 28 ng/mL) on day 3 of admission, he was taken to the cardiac catheterization laboratory. Results of a coronary angiography were normal, but biopsy specimens revealed acute lymphocytic myocarditis (Fig 1), and a polymerase chain reaction (PCR) performed on the tissue was positive for parvovirus (Table 1). Parvovirus serology was not performed during admission. He was discharged with normal LV function (EF 62%) after 4 days. Ventricular function on his follow-up echocardiogram 3 weeks later remained normal, and the ECG revealed complete normalization. Significant hyperenhancement along the posterior lateral and anterior walls of the left ventricle (extending from the epicardium into the midmyocardial region) was demonstrated in an MRI performed 2 months after hospital discharge (Fig 2). A comparison of the 2 myocarditis presentations is provided in Table 2.

TABLE 1 EMB Viral Panel Performed by the Laboratory at Cincinnati Children's Heart Institute

Adenovirus qualitative PCR
Epstein-Barr virus qualitative PCR
Cytomegalovirus qualitative PCR
Parvovirus qualitative PCR
Respiratory syncytial virus qualitative PCR
Influenza A qualitative PCR
Enterovirus qualitative PCR
Hepatitis C virus qualitative PCR
HHV-6 qualitative PCR

HHV-6, human herpesvirus 6.

DISCUSSION

Unfortunately, pediatric providers who suspect a recurrence of myocarditis have limited evidence to guide patient management because the literature in this domain is

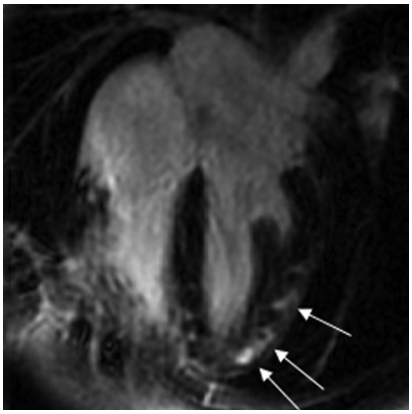

FIGURE 2
Cardiac MRI revealing delayed gadolinium enhancement in the LV free wall, suggestive of patchy myocardial fibrosis. The RV free wall was not nulled by the inversion time. RV, right ventricular.

TABLE 2 Comparison of 2 Presentations With Myocarditis

Initial Findings	First Presentation	Second Presentation
Symptoms	Acute substernal chest pain, orthopnea, and diaphoresis 2-d prodrome of fever, cough, and pharyngitis	Dull central chest and left arm pain 3-d prodrome of fever, myalgia, and pharyngitis
Laboratory findings		
WBC	8.4 K/μL	9.3 K/μL
Neutrophils, %	48	41
Bands, %	20	29
Lymphocytes, %	22	13
CRP	Not performed	4.1 mg/dL
Initial CK (peak CK)	978 (1323) U/L	Not performed
Initial CKMB (peak CKMB)	86.4 (102.1) μg/L	Not performed
Initial troponin (peak troponin)	17.62 (25.96) ng/mL	22.31 (28.27) ng/mL
Diagnostic and imaging findings		
Echocardiogram		
LVEF (biplane), %	55	42
LVIDd	4.27 cm, *z* score −1.62	4.89 cm, *z* score −0.19
ECG	ST segment elevation in inferior leads, T wave inversion in lateral leads	ST segment elevation in anterolateral leads and inferior leads
MRI	Anteroseptal and midventricular edema	Posterior lateral and anterior LV wall hyperenhancement extending from the epicardium into the midmyocardial region[a]
EMB	Not performed	Acute lymphocytic myocarditis and PCR performed on the tissue was positive for parvovirus

CRP, C-reactive protein; LVEF, left ventricular ejection fraction.
[a] Study performed 2 mo after presentation.

sparse.[7] Recurrent myocarditis is considered to be extremely rare, and all but 1 reported case have involved adult patients.[7] These diagnoses were made clinically, with only a few of these citing MRI or biopsy results.[7,11–13]

Myocarditis is often a clinical diagnosis, which poses a challenge because of its diverse clinical presentation. Some children report nonspecific, benign symptoms, whereas others' symptoms mimic myocardial ischemia. Another subset of patients present with hemodynamic collapse or sudden death.[4,14] The Dallas criteria, which are considered the diagnostic gold standard, require endomyocardial biopsy (EMB).[15] This is inconsistently performed in children because of the risks of perforation, arrhythmia, or hemodynamic compromise associated with the procedure.[14,16] As a result, pediatric providers are often reliant on clinical, laboratory, and imaging data to make the diagnosis. There is now an emerging trend in the use of MRI in evaluating children with possible myocarditis.[5] Nevertheless, it is generally felt that unless MRI is unequivocal, a definitive diagnosis requires histology.[17,18] When faced with a potential recurrence of myocarditis, these diagnostic challenges are compounded by the lack of reported cases in the literature.

In 2014 Chikly et al[11] described a 37-year-old who suffered 2 episodes of myocarditis 5 years apart, each occurring within days of group A streptococcal pharyngitis. No biopsy was performed at either presentation, although during his second admission, myocarditis was confirmed with MRI.

Yoshimizu et al[19] reported a 52-year-old with 2 episodes of recurrent, fulminant myocarditis spaced 16 years apart. On both occasions, the patient required mechanical circulatory support and the diagnosis was made by using clinical and echocardiographic data, with significantly elevated serum influenza titers. He had documented recovery of LV function between episodes.

Xu et al[12] reported cases of 2 men (39 and 49 years old) who both were initially diagnosed with recurrent myocardial infarctions over the course of 6 to 10 years, with associated viral symptoms. Results of coronary angiography for both patients were normal. Both eventually had MRIs during their most recent presentations, and each MRI revealed myocardial edema with delayed gadolinium enhancement, which is in keeping with myocarditis.

Kanazawa et al[13] described a 42-year-old with 4 biopsy specimen–proven episodes of myocarditis over a period of 14 years.

At present, there exists a solitary report of recurrent myocarditis

in a pediatric patient. Lee et al[7] described a case of an 8-year-old who had 3 episodes of acute heart failure requiring inotropic support over a period of 3 years. Each episode occurred within a week of the onset of viral symptoms. The initial diagnosis was based on an elevated troponin level and diminished LV function by echocardiography. EMB was performed but was described as nondiagnostic. Subsequent presentations were similar and the patient had recovery of LV function between episodes. With the third presentation, a nasopharyngeal swab was H1N1 positive and the diagnosis of recurrent viral myocarditis was made. The patient suffered a bradycardic cardiac arrest on the second day of the third admission and did not survive. Interestingly, myocardial samples obtained during autopsy did not meet the Dallas criteria for myocarditis.

In the existing literature, many of these reported adult cases are unable to exclude conditions such as chronic myocarditis and/or cardiomyopathy that could mimic recurrent myocarditis. Patients who develop a dilated cardiomyopathy phenotype after an initial episode of myocarditis could potentially re-present with heart failure symptoms during a subsequent viral illness, especially if their cardiomyopathy goes unrecognized. Although parvovirus B19 has been found in biopsy specimens from patients with dilated cardiomyopathy who lacked clinical evidence of acute myocarditis,[20,21] our patient's clinical presentations and echocardiogram findings were much more consistent with an acute process.

His symptoms, ventricular function, biomarkers, and ECG results completely normalized between the episodes of myocarditis, suggesting that these were 2 discrete, acute events. Furthermore, the complete normalization of the echocardiogram results for our patient between these admissions in the absence of LV dilation supports recurrent myocarditis instead of dilated cardiomyopathy. In the context of a high clinical suspicion for myocarditis, parvovirus was felt to be the most likely causative agent for the second episode, although the chronicity of this infection cannot be known definitively.

This case is not only unique in the pediatric literature; with it, we illustrate several key points: recurrent myocarditis is a disease that can occur in pediatric populations, early recognition can lead to appropriate and timely supportive care, and identifying this condition may guide patients' long-term follow-up and potentially aid in risk stratification.

CONCLUSIONS

Recurrent myocarditis is a rare phenomenon with only a few true cases in the existing literature. Those reported primarily involve adults and include inconsistent diagnostic data. Although uncommon, recurrent myocarditis should be considered in children who re-present with clinical and diagnostic features of the disease. Early recognition of myocarditis is key because there is the potential for rapid deterioration of these patients, with a relatively high number requiring mechanical circulatory support.[5] Cardiac MRI and/or EMB can assist in reaching the diagnosis, and in fact, are probably the most highly specific investigations. EMB has been shown to be safe in young children if performed by experienced providers and should be considered in patients with severe or chronic symptoms.[17,18] Future studies may be helpful to establish risk factors for and long-term outcomes of recurrent myocarditis.

ABBREVIATIONS

CK: creatine kinase
CKMB: creatine kinase-MB
ECG: electrocardiogram
ED: emergency department
EF: ejection fraction
EMB: endomyocardial biopsy
LV: left ventricular
LVIDd: left ventricular end-diastolic internal dimension
PCR: polymerase chain reaction
WBC: white blood cell

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Pediatrics 2018;141;
DOI: 10.1542/peds.2016-4096 originally published online February 8, 2018;

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